

# **Report to SAGE on Evidence Supporting Measles Revaccination for HIV-infected Children Receiving Highly Active Antiretroviral Therapy**

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## **Introduction**

Human immunodeficiency virus (HIV)-infected children are at increased risk of measles morbidity and mortality and could play a role in sustaining measles virus transmission in regions of high HIV prevalence. Protective antibody concentrations wane following measles vaccination of HIV-infected children as a consequence of impaired immunity. Until the widespread introduction of antiretroviral therapy, the high mortality rate of HIV-infected children prevented the build-up of a sizeable pool of measles susceptible children. Highly active antiretroviral therapy (HAART) is effective in prolonging survival in HIV-infected children by suppressing viral replication and restoring immune function. However, immune reconstitution in children is primarily achieved through the generation of naïve T and B lymphocytes rather than the expansion of memory lymphocytes and antiretroviral therapy does not restore measles vaccine-induced immunity established prior to therapy. As a consequence, HIV-infected children are at increased risk of measles morbidity and mortality despite measles vaccination. In countries with a high prevalence of HIV infection, susceptible children receiving HAART could become sufficiently numerous to sustain measles virus transmission despite high levels of measles vaccine coverage.

In 2012, the Advisory Committee on Immunization Practices recommended measles revaccination of persons with perinatal HIV infection who were vaccinated before establishment of effective antiretroviral therapy with two appropriately spaced doses of MMR vaccine once effective ART has been achieved. In low and middle-income countries, particularly those in sub-Saharan Africa that bear the greatest burden of pediatric HIV infection, antiretroviral treatment programs have scaled-up dramatically, increasing access to life-prolonging treatment for HIV-infected children. To protect these children against measles, and ensure high levels of population immunity, revaccination with MCV after immune reconstitution with HAART should be recommended (Rainwater-Lovett 2010).

## **Current recommendations on measles vaccination of HIV-infected children**

### World Health Organization

The World Health Organization (WHO) position paper on measles vaccines recommends measles vaccination of HIV-infected children who are not severely immunosuppressed and measles vaccine may be administered as early as six months of age in regions of high measles incidence (World Health Organization 2009). Importantly, the position paper makes no recommendations on revaccination after immune reconstitution with antiretroviral therapy. The WHO position paper on measles vaccines states:

*Given the severe course of measles in patients with advanced HIV infection, measles vaccination should be routinely administered to potentially susceptible, asymptomatic HIV-positive children and adults. Vaccination may even be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to conventional definitions. In areas where there is a high incidence of both HIV infection and measles, the first dose of MCV may be offered as early as age 6 months. Two additional doses of measles vaccine should be administered to these children according to the national immunization schedule.*

### Advisory Committee on Immunization Practices (ACIP)

In 2012, the ACIP recommended measles revaccination of persons with perinatal HIV infection who were vaccinated before establishment of effective antiretroviral therapy with two appropriately spaced doses of MMR vaccine once effective ART has been established (McLean 2013). The ACIP recommendation states:

*Persons with perinatal HIV infection who were vaccinated with measles-, rubella-, or mumps-containing vaccine before establishment of effective ART should receive 2 appropriately spaced doses of MMR vaccine (i.e., 1 dose now and another dose at least 28 days later) once effective ART has been established unless they have other acceptable current evidence of measles, rubella, and mumps immunity. Established effective ART is defined as receiving ART for  $\geq 6$  months in combination with CD4 percentages  $\geq 15\%$  for  $\geq 6$  months for persons aged  $\leq 5$  years and CD4 percentages  $\geq 15\%$  and CD4 count  $\geq 200$  lymphocytes/mm<sup>3</sup> for  $\geq 6$  months for persons aged  $> 5$  years. When only CD4 counts or only CD4 percentages are available for those aged*

*>5 years, the assessment of established effective ART can be on the basis of the CD4 values (count or percentage) that are available. When CD4 percentages are not available for those aged ≤5 years, the assessment of established effective ART can be on the basis of age-specific CD4 counts at the time CD4 counts were measured (i.e., established effective ART is defined as receiving ART for ≥6 months in combination with meeting age-specific CD4 count criteria for ≥6 months: CD4 count >750 lymphocytes/mm<sup>3</sup> while aged ≤12 months and CD4 count ≥500 lymphocytes/mm<sup>3</sup> while aged 1 through 5 years).*

The ACIP based this recommendation on a review of the evidence on the immune responses to MMR vaccine among HIV-infected persons:

*Before the availability of effective ART, responses to MMR vaccine among persons with HIV infection were suboptimal. Although response to revaccination varied, it generally was poor. In addition, measles antibodies appear to decline more rapidly in children with HIV infection than in children without HIV infection.*

*Memory B cell counts and function appear to be normal in HIV-infected children who are started on effective ART early (aged <1 year), and responses to measles and rubella vaccination appear to be adequate. Measles antibody titers were higher in HIV-infected children who started effective ART early compared with HIV-infected children who started effective ART later in life. Likewise, vaccinated HIV-infected children who initiated effective ART before vaccination had rubella antibody responses similar to those observed in HIV-uninfected children.*

*Despite evidence of immune reconstitution, effective ART does not appear to reliably restore immunity from previous vaccinations. Perinatally HIV-infected youth who received MMR vaccine before effective ART might have increased susceptibility to measles, mumps, and rubella compared with HIV-exposed but uninfected persons. Approximately 45%–65% of previously vaccinated HIV-infected children had detectable antibodies to measles after initiation of effective ART, 55%–80% had detectable antibodies to rubella, and 52%–59% had detectable antibodies to mumps. However, revaccination with MMR vaccine after initiation of effective ART increased the proportion of HIV-infected children with detectable antibodies to measles, rubella,*

*and mumps (64%–90% for measles, 80%–100% for rubella, and 78% for mumps). Although, data on duration of response to revaccination on effective ART are limited, the majority of children had detectable antibodies to measles (73%–85%), rubella (79%), and mumps (61%) 1–4 years after revaccination. [Citations removed from text]*

#### Paediatric European Network for Treatment of AIDS

In 2012, the Paediatric European Network for Treatment of AIDS and Children's HIV Association published guidelines on vaccination of HIV-infected children, including revaccination (Menson 2012). Immunological status and antibody concentrations were used to guide policy recommendations. For HIV-infected children without evidence of immune suppression, based on CD4<sup>+</sup> T lymphocyte counts and percentages, and with serologic evidence of protective antibody concentrations, no modification to the immunization schedule is required. For children with no or mild immune suppression who lack evidence of serologic protection, revaccination is recommended followed by repeat measurement of antibody concentrations. For children with moderate or severe immunosuppression and lack of protective antibody concentrations, revaccination is recommended after immune reconstitution on antiretroviral therapy, approximately six months after normalization of CD4<sup>+</sup> T lymphocyte count and consistent with the recommendation to withdraw prophylaxis for pneumocystis pneumonia. Although feasible in much of the European region, a policy based on serological testing is not applicable to much of sub-Saharan Africa and Asia.

#### **Evidence in Support of the Recommendations**

*An increasingly large number of HIV-infected children will receive antiretroviral therapy*  
As of December 2013, an estimated 740,000 HIV-infected children in low and middle-income countries were receiving antiretroviral therapy, with 630,300 (85%) residing in Africa (World Health Organization). These children represent only 23% (21–25%) of the estimated 3.2 million (2.9 to 3.5 million) children younger than 15 years of age living with HIV (Figure 1).

#### *Measles case fatality ratio is higher in HIV-infected children*

A report from the Centers for Disease Control and Prevention published in 1988 first highlighted the unusual and severe clinical manifestations of measles in five HIV-infected children (a sixth child was reported but subsequently determined not to be HIV-

infected) (Centers for Disease Control and Prevention 1988). Additional case reports from the United States confirmed the unusual clinical manifestations and severity of measles in HIV-infected persons, with a case fatality ratio (CFR) of 32% among 19 HIV-infected children with measles (Moss 1999). These case series were subject to reporting biases and overestimation of the CFR, although they were consistent with reports from sub-Saharan Africa. In the Democratic Republic of Congo, the CFRs among 16 HIV-seropositive and 298 seronegative children hospitalized with measles were high but similar (31% compared to 28%) (Sension 1988). Another group of investigators in Lusaka, Zambia reported that the measles CFR for HIV-seropositive children between 9 and 59 months of age was significantly higher (28%) than for HIV-seronegative children (8.3%), although they did not distinguish HIV-infected from HIV-seropositive (i.e. exposed but uninfected) children (Oshitani 1996).

The largest prospective study of measles mortality among hospitalized HIV-infected children, in which infection with both measles virus and HIV infection were laboratory-confirmed, was conducted at the University Teaching Hospital in Lusaka, Zambia between 1998 and 2003 (Moss 2002, Moss 2008). Of 1474 enrolled children, 1227 (83%) had confirmed measles and known HIV infection status. Almost one-third of the HIV-infected children with measles were younger than nine months of age, compared with one-quarter of the uninfected children ( $P = 0.07$ ). Death occurred during hospitalization in 23 HIV-infected children (12.2%) and 45 HIV-1-uninfected children (4.3%,  $P < 0.001$ ) with measles. After adjusting for age, sex and measles vaccination status, HIV infection (OR 2.5, 95% CI: 1.4, 4.6) and the presence of a desquamating rash (OR 2.2, 95% CI: 1.3, 3.6) were significant predictors of measles mortality. Thus, co-infection with HIV more than doubled the odds of death in hospitalized children with measles. HIV-infected children with measles were more likely to be younger than 6 and 9 months of age compared to HIV-uninfected children, consistent with the observation that infants born to HIV-infected women lose passively-acquired, protective maternal antibodies at an earlier age (Scott 2007). HIV-infected children also were more likely to have a history of measles vaccination, consistent with the hypothesis that HIV-infected children lose protective immunity after immunization.

Subsequent studies have confirmed the increased mortality due to measles in HIV-infected children. HIV-infection was associated with increased mortality in a study of

1274 children hospitalized with measles-related disease in a pediatric intensive care unit in Cape Town, South Africa during the measles outbreak of 2010 (Coetzee 2014).

*Measles seroprevalence is lower in HIV-infected than uninfected children after vaccination*

The Global Advisory Committee on Vaccine Safety commissioned a systematic review and meta-analysis to identify and synthesize evidence about the safety, immunogenicity and effectiveness of measles vaccination in HIV-infected children (Global Advisory Committee on Vaccine Safety 2009; Scott 2011) (Figure 2). The Committee report was published in 2009 and summarized the evidence of the systematic review and meta-analysis and drew several conclusions:

*A total of 8 electronic databases were searched for studies published until February 2009 relating to measles vaccination in HIV-positive children. Altogether, 723 articles were identified, of which 25 studies with comparison groups (involving 4519 vaccinated children) and 1 case-report were eligible for inclusion. Another 13 studies without comparison groups (involving 690 vaccinated children) were also examined for data on adverse events.*

*Serological assessments of measles antibody titres after vaccination showed that measles vaccination at the age of 6 months resulted in similar levels of antibody in HIV-positive children and children who had not been exposed to HIV; by the age of 9 months, fewer HIV-positive children (with severity of disease ranging from no clinical signs of AIDS to groups where 71% were symptomatic) responded to measles vaccine than did children who had not been exposed to HIV. After measles vaccination at age 6 months, children who had initially tested HIV-positive owing to maternal antibodies but were subsequently found to be uninfected, were slightly more likely to have developed antibodies than children who had not been exposed to HIV. Two studies suggested that the antibody response in HIV-positive children waned faster than it did in children who were not infected with HIV. **There were scant data about the effects of highly active antiretroviral treatment (HAART) on responses to measles vaccination [emphasis added],** and the possibility of comparing vaccinated children to unvaccinated HIV-positive children was limited. Data relating to clinical efficacy against measles were also scarce.*

*Based on these findings the Committee drew the following conclusions.*

- *Measles vaccine appears to be immunogenic in the majority of HIV-positive children. Important areas for further research include determining the duration of immunity and protection, **and whether there is a benefit to administering a second dose of measles vaccine to HIV-positive children [emphasis added]**.*
- *On the basis of the literature reviewed, the Committee considers that there is no need to modify WHO's recommendation on measles vaccination in HIV-positive children.*
- *The recommendation on the use of measles vaccines indicates that it is contraindicated in people who are severely immunocompromised. This reflects the risk–benefit ratio, since children with low CD4 cell counts might derive little benefit from the vaccine.*
- *Studies should be conducted to investigate remaining concerns. These include studies to determine the etiology of pneumonia in HIV-positive infants (no studies have examined for measles virus as the etiological agent of pneumonia in HIV-positive children), to compare morbidity and mortality among HIV-positive children with and without measles vaccination, **to determine the immunogenicity of measles vaccine in HIV-positive children on HAART, and to evaluate the duration of immunity and whether there is an added benefit in administering a second dose of measles vaccine to HIV-positive children [emphasis added]**.*

To provide several illustrative examples, one study of standard-titer measles vaccine at 6 and 9 months of age found 59% of HIV-infected children were measles seropositive after vaccination at 6 months but only 64% after vaccination again at 9 months of age (Helfand 2005; Fowlkes 2011). In contrast, 88% of 50 HIV-infected children in Zambia developed measles antibody levels  $\geq 120$  mIU/mL within six months of measles vaccination at nine months of age compared with 94% of 98 HIV-seronegative children and 94% of 211 HIV-seropositive but uninfected children ( $P = .3$ ) (Moss 2007). However, these HIV-infected children had lower antibody avidity (Nair 2009) and experienced waning antibody levels and lower frequency of protective immunity by 2 to 3 years of age (see below).

In cross-sectional studies among various populations, the prevalence of measles antibody after vaccination varied widely, ranging from 17% to 100%. An association between lack of measles virus-specific antibodies after vaccination and low CD4<sup>+</sup> T lymphocyte count was documented in some studies. The response to a second dose of measles vaccine was variable, but generally poor, in five studies of HIV-infected children not receiving antiretroviral therapy.

The systematic review was updated by Nicky Mehtani based on articles published after the availability of HAART in 1996 through February 2015. Twelve papers were selected after screening 2,324 records (Figure 3). For the five studies reporting on children vaccinated against measles at nine months of age, the seroprevalence ratio comparing HIV-infected to uninfected children ranged from 0.44 to 1.05, although the confidence intervals for individual studies were wide. Heterogeneity across studies precluded meta-analysis. The updated systematic review did not find evidence contradicting the earlier review.

#### *Protective antibody levels wane in HIV-infected children not receiving HAART*

Two prospective studies documented waning measles antibody levels in HIV-infected children not receiving antiretroviral therapy. In a prospective study of the immunogenicity of measles vaccine administered at 9 months of age to HIV-infected and uninfected children in Lusaka, Zambia, 88% of 50 HIV-infected children developed antibody levels of  $\geq 120$  mIU/mL, compared with 94% of 98 HIV-unexposed children and 94% of 211 HIV-exposed, uninfected children, suggesting a good primary response to measles vaccine (Moss 2007). By 27 months after vaccination, however, only half of the 18 HIV-infected children who survived and returned for follow-up maintained measles antibody levels  $\geq 120$  mIU/mL, compared with 89% of 71 uninfected children (Figure 5).

Low measles seroprevalence at the time of starting antiretroviral treatment provides supportive evidence that antibody levels wane in HIV-infected children not receiving antiretroviral therapy. In the largest study, involving HIV-infected children aged 2 to 19 years receiving antiretroviral therapy in the United States, only 52% of 193 children had protective antibody concentrations at the time of starting antiretroviral therapy (Abzug



2012). Among 61 HIV-infected Zambian children 9 to 60 months of age starting antiretroviral therapy, only 23% were measles seropositive (Rainwater-Lovett 2013).

*Measles vaccine effectiveness is reduced among HIV-infected children*

Limited data are available on measles vaccine effectiveness among HIV-infected children, including those receiving antiretroviral therapy. A study in Johannesburg, South Africa found lower levels of vaccine effectiveness among HIV-infected compared with uninfected persons during measles outbreaks from 2003 to 2005, although few HIV-infected persons were studied (McMorrow 2009). Of 109 persons hospitalized with measles, 57 were eligible for measles vaccination and of these 27 (47.4%) were vaccinated. Fourteen (12.8%) were HIV infected, 46 (42.2%) were HIV uninfected, and 49 (45.0%) had unknown HIV infection status. Among children aged 12-59 months, measles vaccine effectiveness was 85% (95% CI: 63, 94) for all children, 63% for HIV-infected children, 75% for HIV-uninfected children, and 96% for children with unknown HIV infection status.

*Antiretroviral therapy does not restore measles immunity in the absence of revaccination*

In a study of the impact of HAART on measles vaccine immunogenicity in Lusaka, Zambia, HAART was not associated with measles seroconversion in 46 children who were seronegative at enrollment nor was there a trend indicating that seroconversion was more likely with increased time on HAART after adjusting for baseline age and CD4<sup>+</sup> T lymphocyte percentage (Rainwater-Lovett 2013).

*Antiretroviral therapy improves responses to measles vaccine*

Several studies have been conducted on the response to measles vaccination or revaccination after initiating HAART (Table 1) and suggest that children receiving HAART are more likely to respond to revaccination than children not receiving HAART. In six published studies, measles seroprevalence following revaccination of HIV-infected children receiving antiretroviral therapy ranged from 64% to 95% within the first three months after vaccination, with a mean of 83%. The two largest studies also had longer follow-up. In a study of 51 HIV-infected children receiving highly active antiretroviral therapy in Thailand, measles seroprevalence was 90% one month after measles revaccination and 85% three years after revaccination. In a study of 193 HIV-infected children receiving highly active antiretroviral therapy in the United States, measles

seroprevalence was 89% eight weeks after measles revaccination and 80% 80 weeks after revaccination. These two studies provide the best evidence of the long-term immunogenicity of measles revaccination in children receiving highly active antiretroviral therapy. Further support for this conclusion comes from a study of 428 HIV-infected children 7 to 15 years of age in the United States that found that the number of measles vaccine doses while receiving antiretroviral therapy was positively associated with seroprotection (Siberry 2015).

*A recommendation to provide an additional dose of MCV to HIV-infected children receiving antiretroviral therapy is consistent with current understanding of the impact of HIV on the developing immune system*

Our understanding of the impact of HIV-infection on the developing immune system is consistent with observations that long-term humoral immune responses are impaired in HIV-infected children, including responses to vaccine antigens (Rainwater-Lovett 2011). HIV infection results in increased activation of CD4<sup>+</sup> and CD8<sup>+</sup> T cells as well as CD4<sup>+</sup> T cell death (Buechler 2015). Immune activation leads to a decreased proportion of naïve T cells and increased proportions of memory, effector and exhausted phenotypes (Rainwater-Lovett 2014b). Hypergammaglobulinemia and poor serologic responses upon subsequent antigen exposure is a consequence of non-specific activation and depletion of resting memory B cells. Antiretroviral therapy can restore resting memory B cell percentages to normal levels (Rainwater-Lovett 2014a), necessary for long-term antibody responses following vaccination.

The age of HIV acquisition affects immune reconstitution following highly active antiretroviral therapy (Rainwater-Lovett 2011). Thymic involution over the lifespan decreases the rate of naïve T cell emigration, resulting in memory T cell expansion as the dominant mechanism for T cell reconstitution in adults. Immunological memory in perinatally-infected children may be limited by skewing of the T cell response toward effector phenotypes, further contributing to immune reconstitution with naïve T cells after initiation of antiretroviral therapy. Exposure to vaccinations and infections prior to HIV infection, as for HIV-infected adolescents and adults, or after HIV infection, as in perinatally-infected children, influences whether immunologic memory will be retained after initiation of antiretroviral therapy due to the ability to expand memory T and B cells.

*Mathematical models suggest potential accumulation of measles susceptible HIV-infected following introduction of antiretroviral therapy, and increased number of measles cases, in regions of high HIV-prevalence in the absence of an additional dose of MCV*

Two published models explored the impact of HIV infection on measles population immunity, one of which included the effect of antiretroviral therapy. The first derived parameter estimates from a literature review and incorporated these in a simple model to estimate the impact of HIV infection on population immunity due to measles vaccine (not wild-type measles virus infection) (Helfand 2005). The model suggested that HIV infection could result in a 2-3% increase in the proportion of the birth cohort susceptible to measles. However, this increase, due to higher rates of primary and secondary vaccine failure among HIV-infected children, was mitigated by the high mortality rate, with the implication that prolonged survival following antiretroviral therapy would result in a higher proportion of children susceptible to measles although the model did not investigate this scenario.

The second model explicitly simulated the introduction of antiretroviral therapy on population immunity to measles virus (Scott 2008). An age-structured, deterministic compartmental model of measles virus transmission in a developing country was extended to incorporate a subpopulation of HIV-infected children. The model suggested that prior to the introduction of antiretroviral therapy, HIV-infection has little impact on the transmission dynamics of measles virus, consistent with empirical findings (Lowther 2009). As with the first model, high mortality rates in HIV-infected children without access to treatment counteract the higher rates of vaccine failure, shorter duration of maternal antibody protection and potential longer duration of infectiousness in HIV-infected children (Permar 2003, Riddell 2007) , as many of these children die before they are able to contribute to measles virus transmission. However, introduction of antiretroviral therapy into the model, modelled as prolonged survival without an increase in measles immunity, resulted in an increase in measles prevalence. The yearly force of infection increased from 11.8% without antiretroviral therapy to 15.5% with antiretroviral therapy starting at one year of age. This resulted in an increased prevalence of measles from 23.9 to 31.4 per 100,000 persons. The proportion of measles cases that were HIV-infected increased from 12% without antiretroviral therapy to 29% with therapy. Seven percent of infants acquired infection before the age of routine vaccination (nine months) in the population with antiretroviral therapy compared to 5.5% without therapy. By 25

years of age, the proportion immune as a result of infection with wild-type measles virus increased from 35% without antiretroviral therapy to 42% with treatment. Less than 0.1% of the children with wild-type measles virus immunity were HIV-infected without treatment compared to 17.5% with antiretroviral therapy. In summary, introduction of antiretroviral therapy led to an increase in measles virus transmission and thus to both an increased prevalence of measles in all age groups, including children younger than 9 months of age, and HIV-infected children constituted a larger proportion of all measles cases when antiretroviral therapy was available.

Two observational studies identified spatial clustering of measles in communities with high HIV prevalence or among HIV-infected children, potentially supporting the model findings. The South African measles outbreak between 2009 and 2011 was associated with the build-up of a susceptible population owing to poor vaccine coverage, high prevalence of HIV infection and high population density (Sartorius 2013). In Lusaka, Zambia, a space-time cluster among HIV-infected children was identified during an endemic period from 1998 to 2003 (Pinchoff 2015). This cluster occurred prior to the introduction of national supplemental immunization activities and during a period between seasonal peaks in measles incidence. In contrast, three sequential and spatially contiguous clusters of measles cases were identified during the 2010 outbreak but no clustering among HIV-infected children was identified.

#### *Measles vaccine is safe in HIV-infected children*

As described above, the Global Advisory Committee on Vaccine Safety commissioned a systematic review and meta-analysis to identify and synthesize evidence about the safety of measles vaccination in HIV-infected children (Global Advisory Committee on Vaccine Safety 2009; Scott 2011). The Committee report was published in 2009 and summarized the safety evidence of the systematic review and drew several conclusions:

*Adverse events were not mentioned in 20 of 39 studies. In the 19 studies that described adverse events, 17 reported no serious or severe adverse events. In 2 prospective studies that reported on adverse events and allowed comparative analysis, there was no increased risk of vaccine-related serious adverse events in HIV-positive children when compared with HIV-exposed but uninfected children or children not exposed to HIV. A total of 8 hospitalizations were*

*reported after vaccination in 457 HIV-positive children enrolled in prospective studies, excluding those events explicitly stated by the authors to be unrelated to vaccination. There were 55 deaths in 387 HIV-positive children who had been vaccinated.*

*Based on these findings the Committee drew the following conclusions.*

- The evidence does not demonstrate a serious risk in using measles vaccine in HIV-positive children. Although millions of doses of measles vaccine have been administered to HIV-positive children, only 1 case report was identified that suggested possible severe adverse events following immunization. However, ascertainment of such events may be incomplete.*
- The literature review documented higher mortality among HIV-positive children who received measles vaccine than among children who were not infected with HIV and who received measles vaccine. However, it seems plausible that most or all of this effect is due to HIV infection alone rather than to measles vaccination. There are many confounding factors that could explain a higher rate of death or severe adverse events following measles vaccination in this population. One possible approach to resolving this issue would be to recommend systematic follow up of children vaccinated against measles in populations with a high prevalence of HIV and to conduct case–control studies of all cases with severe adverse events following measles vaccination in order to assess the possible part played by HIV infection.*
- On the basis of the literature reviewed, the Committee considers that there is no need to modify WHO’s recommendation on measles vaccination in HIV-positive children.*
- The recommendation on the use of measles vaccines indicates that it is contraindicated in people who are severely immunocompromised. This reflects the risk–benefit ratio, since children with low CD4 cell counts might derive little benefit from the vaccine.*
- Studies should be conducted to investigate remaining concerns. These include studies to determine the etiology of pneumonia in HIV-positive infants (no studies have examined for measles virus as the etiological*

*agent of pneumonia in HIV-positive children), to compare morbidity and mortality among HIV-positive children with and without measles vaccination....*

An updated systematic review through February 2015 conducted by Nicky Mehtani, as described above, found no additional evidence of severe adverse events attributable to measles vaccine in HIV-infected children. Deaths after vaccination were reported in six studies, with a case fatality of 19% in 309 HIV-infected children who received measles vaccine. However, no deaths were attributed to measles vaccine and there were no reported cases of pneumonitis, measles inclusion body encephalitis or thrombocytopenia.

Any potential increased risk of adverse events following measles vaccination of HIV-infected children is likely to be substantially lower in children who achieve immune reconstitution following antiretroviral therapy.

*Optimal timing of measles revaccination in relation to antiretroviral therapy*

The optimal timing of measles vaccination after initiation of antiretroviral therapy is not known. Most cross-sectional and prospective studies found that higher CD4<sup>+</sup> T lymphocyte counts and lower HIV viral loads were crudely or independently associated with seropositivity after measles vaccination of HIV-infected children receiving antiretroviral therapy (Sutcliffe 2010), suggesting standard markers of immune reconstitution are associated with improved responses to measles vaccine. Prospective studies of HIV-infected children demonstrated that CD4<sup>+</sup> T lymphocyte percentages achieve levels  $\geq 20\text{-}25\%$  at 9 to 12 months following the start of antiretroviral therapy (Sutcliffe 2010).

*HIV-infected children who start antiretroviral therapy prior to or shortly after the first dose of MCV may not require revaccination*

Age at initiation of antiretroviral therapy in relation to the timing of measles vaccination may be important in enhancing vaccine responses. In one study, children who initiated antiretroviral therapy younger than 12 months of had higher levels of protective immunity than children who initiated antiretroviral therapy later in childhood, with levels of immunity comparable to uninfected children of the same age (Pensiero 2009). Little

data exist on the immunogenicity of measles vaccine in children who start HAART prior to 9 or 12 months of age and their first dose of MCV.

*Revaccination of HIV-infected children should be programmatically feasible*

A policy to provide an additional dose of MCV to HIV-infected children has several important programmatic implications:

1. HIV-infected children receiving antiretroviral therapy receive intensive follow-up and care, most often at clinics devoted to the care of HIV-infected children and adults. HIV-infected children are typically evaluated every 3 months, particularly after the start of antiretroviral therapy. Frequent follow-up visits would facilitate revaccination.
2. The care of HIV-infected children is typically delivered at specialized clinics and not at maternal and child health clinics where routine vaccines are administered. Thus, a policy to revaccinate HIV-infected children against measles will require coordination between the clinics that provide HIV care and those that provide routine immunizations to children.
3. As countries introduce a second dose of measles-containing vaccine, and continue to conduct supplemental immunization activities, some HIV-infected children will be revaccinated against measles after immune reconstitution with antiretroviral therapy through these mechanisms.
4. With increasing emphasis on early diagnosis and treatment of HIV-infected children, some children may start antiretroviral therapy prior to measles vaccination. These children may not require revaccination.

## References

1. Abzug MJ, Qin M, Levin MJ, Fenton T, Beeler JA, Bellini WJ, Audet S, Sowers SB, Borkowsky W, Nachman SA, Pelton SI, Rosenblatt HM; International Maternal Pediatric Adolescent AIDS Clinical Trials Group P1024 and P1061s Protocol Teams. Immunogenicity, immunologic memory, and safety following measles revaccination in HIV-infected children receiving highly active antiretroviral therapy. *J Infect Dis* 2012;206:512-22.
2. Aupibul L, Puthanakit T, Sirisanthana T, Sirisanthana V. Response to measles, mumps, and rubella revaccination in HIV-infected children with immune recovery after highly active antiretroviral therapy. *Clin Infect Dis* 2007;45:637-42.
3. Aupibul L, Puthanakit T, Sirisanthana T, Sirisanthana V. Persistence of measles, mumps, and rubella protective antibodies 3 years after revaccination in HIV-infected children receiving antiretroviral therapy. *Clin Infect Dis* 2010;50:1415-8.
4. Berkelhamer S, Borock E, Elsen C, Englund J, Johnson D. Effect of highly active antiretroviral therapy on the serological response to additional measles vaccinations in human immunodeficiency virus-infected children. *Clin Infect Dis* 2001;32:1090-4.
5. Buechler MB, Newman LP, Chohan BH, Njoroge A, Wamalwa D, Farquhar C. T cell anergy and activation are associated with suboptimal humoral responses to measles revaccination in HIV-infected children on antiretroviral therapy in Nairobi, Kenya. *Clin Exp Immunol*. 2015;181:451-6.
6. Centers for Disease Control and Prevention. Measles in HIV-infected children, United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1988; 37:183-6.
7. Coetzee S, Morrow BM, Argent AC. Measles in a South African paediatric intensive care unit: again! *J Paediatr Child Health*. 2014;50:379-85.
8. Farquhar C, Wamalwa D, Selig S, John-Stewart G, Mabuka J, Majiwa M, Sutton W, Haigwood N, Wariua G, Lohman-Payne B. Immune responses to measles and tetanus vaccines among Kenyan human immunodeficiency virus type 1 (HIV-1)-infected children pre- and post-highly active antiretroviral therapy and revaccination. *Pediatr Infect Dis J* 2009;28:295-9.
9. Fowlkes A, Witte D, Beeler J, Audet S, Garcia P, Curns A, Yang C, Fudzulani R, Broadhead R, Bellini WJ, Cutts F, Helfand RF. Persistence of vaccine-induced measles antibody beyond age 12 months: a comparison of response to one and two



- doses of Edmonston-Zagreb measles vaccine among HIV-infected and uninfected children in Malawi. *J Infect Dis* 2011;204 Suppl 1:S149-57.
10. Global Advisory Committee on Vaccine Safety, report of meeting held 17-18 June 2009. *Weekly Epidemiological Record* 2009;84:325-32.
  11. Helfand RF, Moss WJ, Harpaz R, Scott S, Cutts F. Evaluating the impact of the HIV pandemic on measles control and elimination. *Bull World Health Org* 2005;83:329-337.
  12. Helfand RF, Witte D, Fowlkes A, Garcia P, Yang C, Fudzulani R, Walls L, Bae S, Strebel P, Broadhead R, Bellini WJ, Cutts F. Evaluation of the immune response to a 2-dose measles vaccination schedule administered at 6 and 9 months of age to HIV-infected and HIV-uninfected children in Malawi. *J Infect Dis* 2008;198:1457-65.
  13. Lowther SA, Curriero FC, Kalish B, Shields TM, Monze M, Moss WJ. Population immunity to measles virus and the effect of HIV-1 infection after a mass measles vaccination campaign in Lusaka, Zambia: a cross-sectional survey. *Lancet* 2009;373:1025-32.
  14. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS and the Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62:1-34.
  15. McMorrow ML, Gebremedhin G, van den Heever J, Kezaala R, Harris BN, Nandy R, Strebel P, Jack A, Cairns KL. Measles outbreak in South Africa, 2003-2005. *S Afr Med J*. 2009;99:314-9.
  16. Melvin AJ, Mohan KM. Response to immunization with measles, tetanus, and Haemophilus influenzae type b vaccines in children who have human immunodeficiency virus type 1 infection and are treated with highly active antiretroviral therapy. *Pediatrics* 2003;111:e641-4.
  17. Menson EN, Mellado MJ, Bamford A, Castelli G, Duiculescu D, Marczyńska M, Navarro ML, Scherpbier HJ and Heath PT on behalf of the Paediatric European Network for Treatment of AIDS (PENTA) Vaccines Group, PENTA Steering Committee and Children's HIV Association (CHIVA). Guidance on vaccination of HIV-infected children in Europe. *HIV Medicine* 2012;13:333–336.
  18. Moss WJ, Cutts F, Griffin DE. Implications of the human immunodeficiency virus epidemic for control and eradication of measles. *Clin Infect Dis* 1999; 29:106-12.

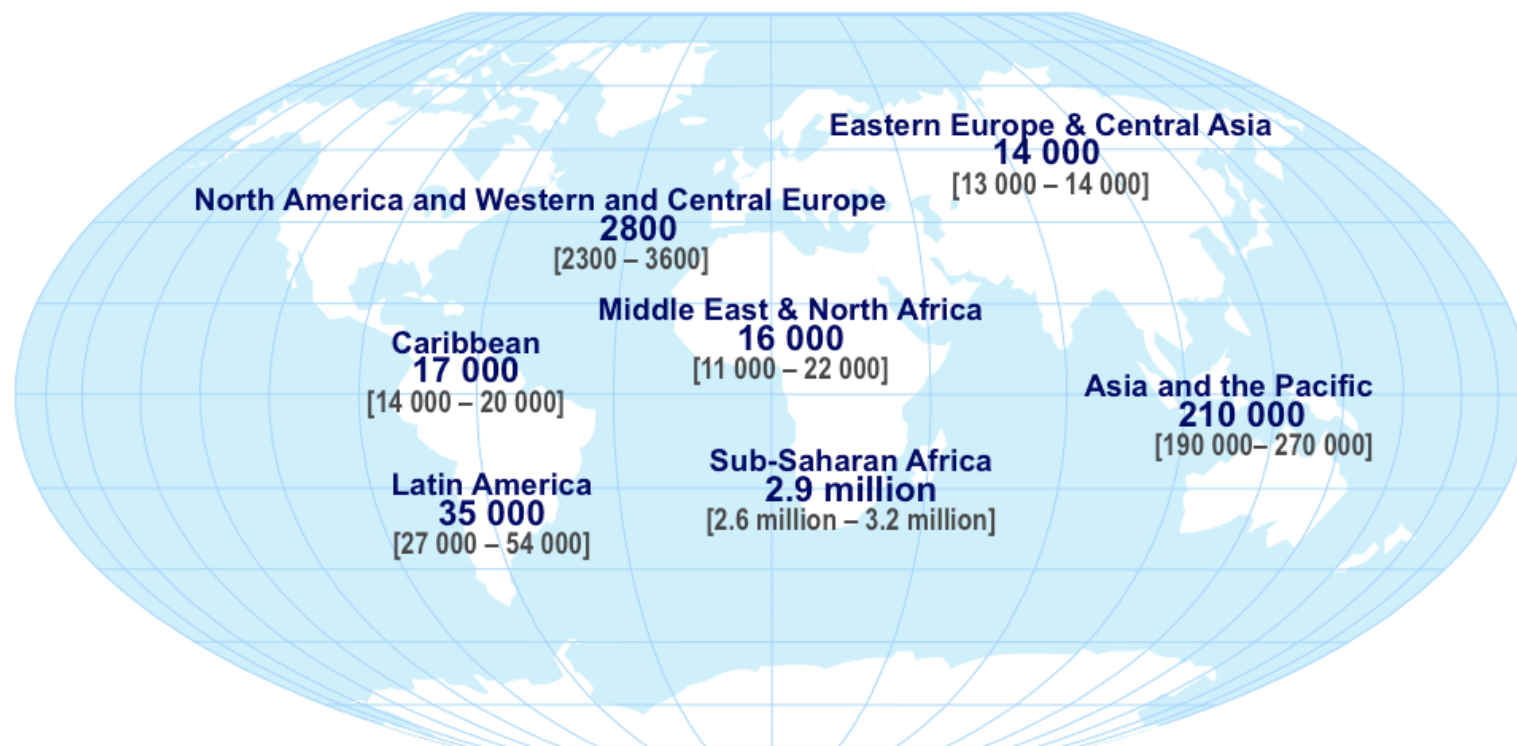
19. Moss WJ, Monze M, Ryon JJ, Quinn TC, Griffin DE, Cutts F. Prospective study of measles in hospitalized human immunodeficiency virus (HIV)-infected and HIV-uninfected children in Zambia. *Clin Infect Dis* 2002; 35:189-96.
20. Moss WJ, Scott S, Mugala N, Ndhlovu Z, Beeler J, Audet S, Ngala M, Mwangala S, Nkonga-Mwangilwa C, Ryon JR, Monze M, Kasolo F, Quinn TC, Cousens S, Griffin DE, Cutts FT. Immunogenicity of standard-titre measles vaccine in HIV-1-infected and uninfected Zambian children: an observational study. *J Infect Dis* 2007;196:347-55.
21. Moss WJ, Fisher C, Scott S, Monze M, Ryon JJ, Quinn TC, Griffin DE, Cutts FT. HIV-1 infection is a risk factor for mortality in hospitalized Zambian children with measles. *Clin Infect Dis* 2008;46:523-527.
22. Nair N, Moss WJ, Scott S, Mugala N, Ndhlovu ZM, Ryon JJ, Monze M, Quinn TC, Cousens S, Cutts F, Griffin DE. HIV-1 infection of Zambian children impairs development and avidity maturation of measles virus-specific IgG following vaccination and infection. *J Infect Dis* 2009;200:1031-8.
23. Oshitani H, Suzuki H, Mpabalwani ME, Mizuta K, Numazaki Y. Measles case fatality by sex, vaccination status, and HIV-1 antibody in Zambian children. *Lancet* 1996; 348:415.
24. Pensiero S, Cagigi A, Palma P, et al. Timing of HAART defines the integrity of memory B cells and the longevity of humoral responses in HIV-1 vertically-infected children. *Proc Natl Acad Sci U S A* 2009; 106: 7939-44.
25. Permar SR, Moss WJ, Ryon JJ, Douek DC, Monze M, Griffin DE. Increased thymic output during acute measles virus infection. *J Virol* 2003;77:7872-7879.
26. Pinchoff J, Chipeta J, Banda GC, Miti S, Shields TM, Curriero FC, Moss WJ. Spatial clustering of measles cases during endemic (1998-2002) and epidemic (2010) periods in Lusaka, Zambia. *BMC Infect Dis* 2015;15:121.
27. Rainwater-Lovett K, Moss WJ. The urgent need for recommendations on re-vaccination of HIV-infected children after successful antiretroviral therapy. *Clin Infect Dis* 2010;51:633-4.
28. Rainwater-Lovett K, Moss WJ. Immunologic basis for revaccination of HIV-infected children receiving HAART. *Future Virol* 2011;6:59-71.
29. Rainwater-Lovett K, Nkamba H, Mubiana-Mbewe M, Bolton-Moore C, Moss WJ. Changes in measles serostatus among HIV-infected Zambian children initiating

- antiretroviral therapy before and after the 2010 measles outbreak: a prospective cohort study. *J Infect Dis* 2013; 208:1747-55.
30. Rainwater-Lovett K, Nkamba H, Mubiana-Mbewe M, Bolton Moore C, Margolick JB, Moss WJ. Antiretroviral therapy restores age-dependent loss of resting memory B cells in young HIV-infected Zambian children. *J Acquir Immune Defic Syndr* 2014;65:505-9. (a)
  31. Rainwater-Lovett K, Nkamba HC, Mubiana-Mbewe M, Bolton Moore C, Margolick JB, Moss WJ. Changes in cellular immune activation and memory T cell subsets in HIV-infected Zambian children receiving HAART. *J Acquir Immune Defic Syndr* 2014;67:455-62. (b)
  32. Riddell MA, Moss WJ, Hauer D, Monze M, Griffin DE. Slow clearance of measles virus RNA after acute infection. *J Clin Virol* 2007;39:312-7.
  33. Sartorius B, Cohen C, Chirwa T, Ntshoe G, Puren A, Hofman K. Identifying high-risk areas for sporadic measles outbreaks: lessons from South Africa. *Bull World Health Organ.* 2013;91:174-83.
  34. Scott P, Moss WJ, Gilani Z, Low N. Safety and immunogenicity of measles vaccine in HIV-infected children: systematic review and meta-analysis. *J Infect Dis* 2011; 204 Suppl 1:S164-78.
  35. Scott S, Moss WJ, Cousens S, Beeler JA, Audet SA, Mugala N, Quinn TC, Griffin DE, Cutts FT. The influence of HIV-1 exposure and infection on levels of passively-acquired antibodies to measles virus in Zambian infants. *Clin Infect Dis* 2007;45:1417-24.
  36. Scott S, Mossong J, Moss WJ, Cutts FT, Cousens S. Predicted impact of the HIV-1 epidemic on measles in developing countries: results from a dynamic age-structured model. *Int J Epidemiol* 2008; 37:356-67.
  37. Sension MG, Quinn T, Markowitz LE, et al. Measles in hospitalized children infected with human immunodeficiency virus. *Am J Dis Child* 1988; 142:1271-2.
  38. Siberry GK, Patel K, Bellini WJ, Karalius B, Purswani MU, Burchett SK, Meyer WA 3rd, Sowers SB, Ellis A, Van Dyke RB; Pediatric HIV AIDS Cohort Study (PHACS); Pediatric HIV AIDS Cohort Study PHACS. Immunity to Measles, Mumps, and Rubella in US Children With Perinatal HIV Infection or Perinatal HIV Exposure Without Infection. *Clin Infect Dis* 2015;61:988-95.

39. Sutcliffe CG, van Dijk JH, Bolton C, Persaud D, Moss WJ. The effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa: a review. *Lancet Infect Dis* 2008;8:477-89.
40. Sutcliffe CG, Moss WJ. Do HIV-infected children receiving HAART need to be revaccinated? a review of the literature. *Lancet Infect Dis* 2010;10:630-42.
41. World Health Organization: <http://www.who.int/hiv/data/en/>
42. World Health Organization. Measles vaccines: WHO position paper. *Wkly Epidemiol Rec* 2009;84:349-60.

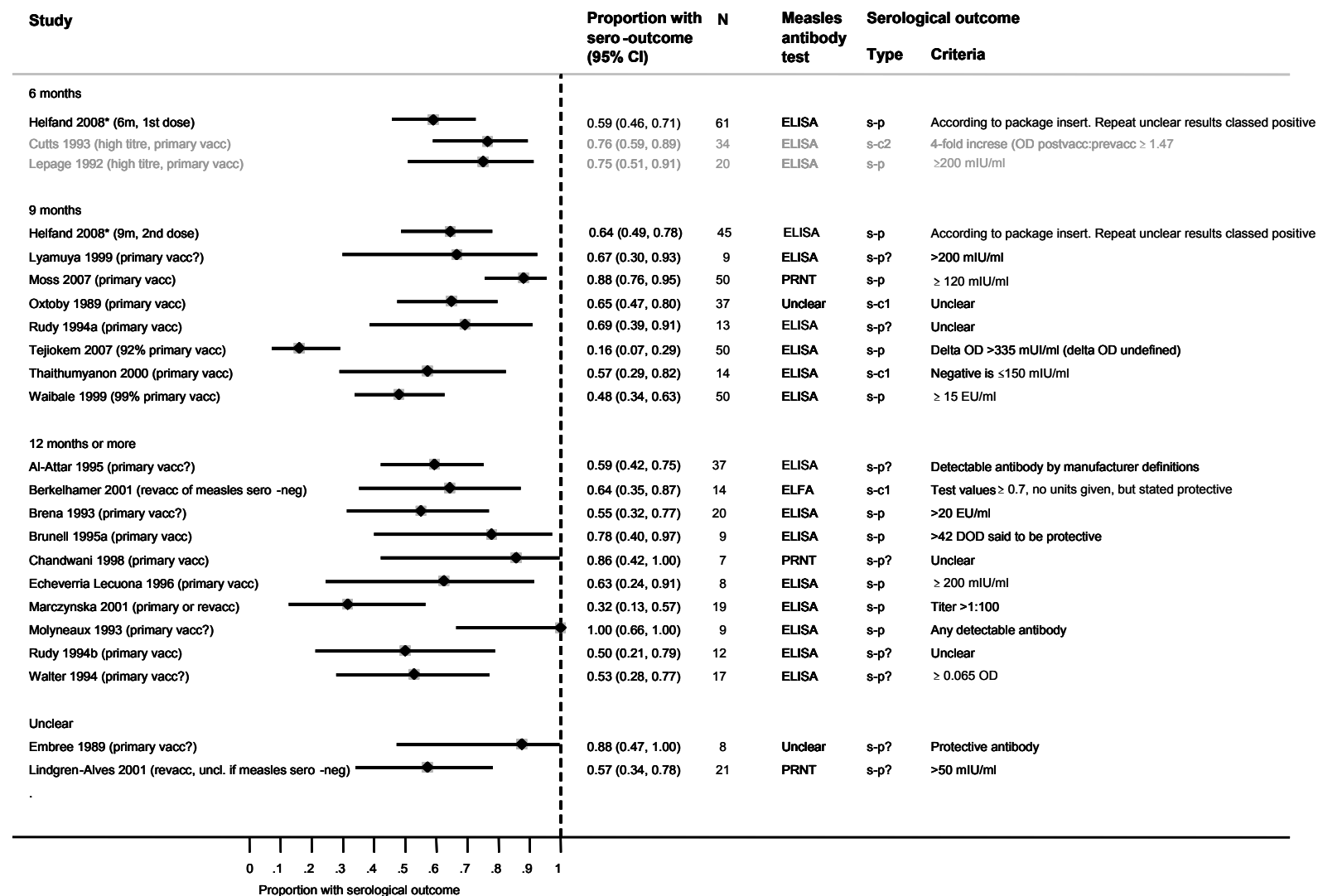
**Figure 1:** Children living with HIV infection in 2013

## Children (<15 years) estimated to be living with HIV | 2013



**Total: 3.2 million [2.9 million – 3.5 million]**

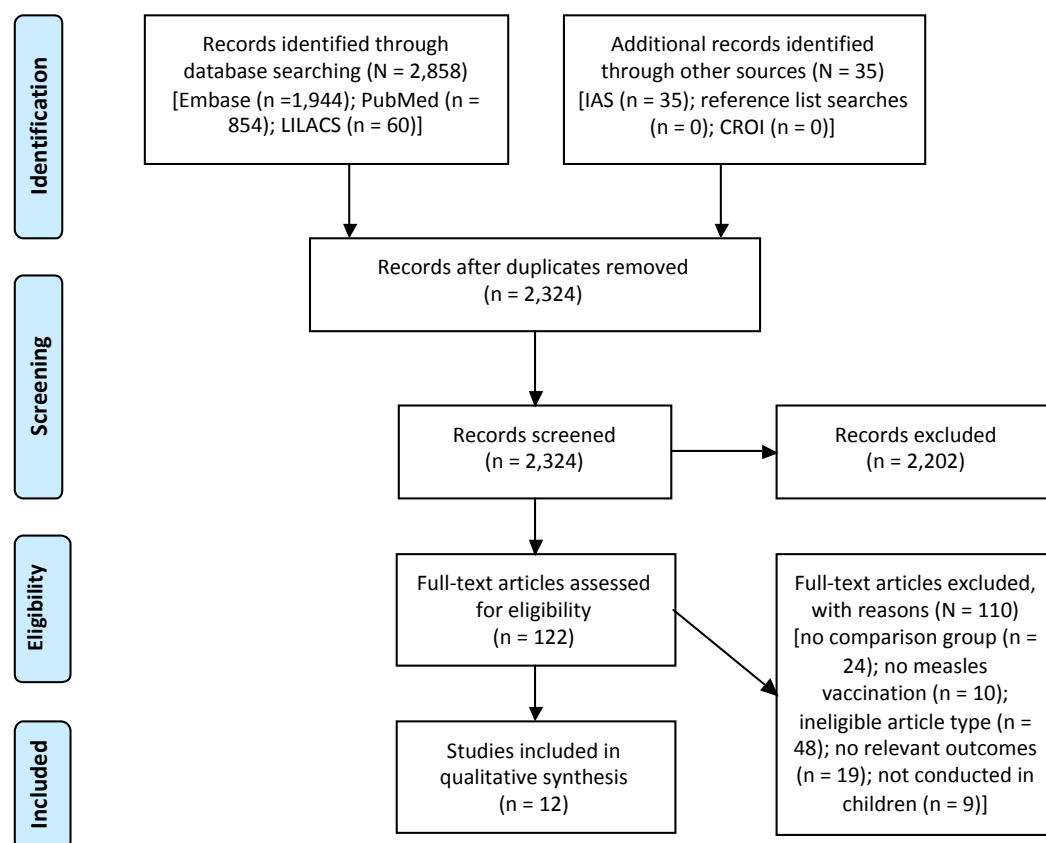
**Figure 2:** Seropositivity or seroconversion after measles vaccination in HIV-infected children.



Source: Scott P, Moss WJ, Gilani Z, Low N. Safety and immunogenicity of measles vaccine in HIV-infected children: systematic review and meta-analysis. J Infect Dis 2011; 204 Suppl 1:S164-78.

\*Results are from the same study after vaccination at 6 and 9 months of age; s-p, seropositivity; s-p?, unclear if those seropositive prior to vaccination are excluded; s-c1, seroconversion from negative to positive; s-c2, seroconversion with 4-fold rise in titer; OD, optical density; change in OD, delta optical density ((mean of 2 viral antigen determinations - mean of 2 controls) x 1000); EU, ELISA units. a Studies where more than 75% of vaccinated children were available for immunogenicity analyses b Studies where blood was drawn for measles serology less than 6 months after vaccination c Studies where children received highly active antiretroviral therapy (HAART) c? Studies where it is not clear if children received HAART

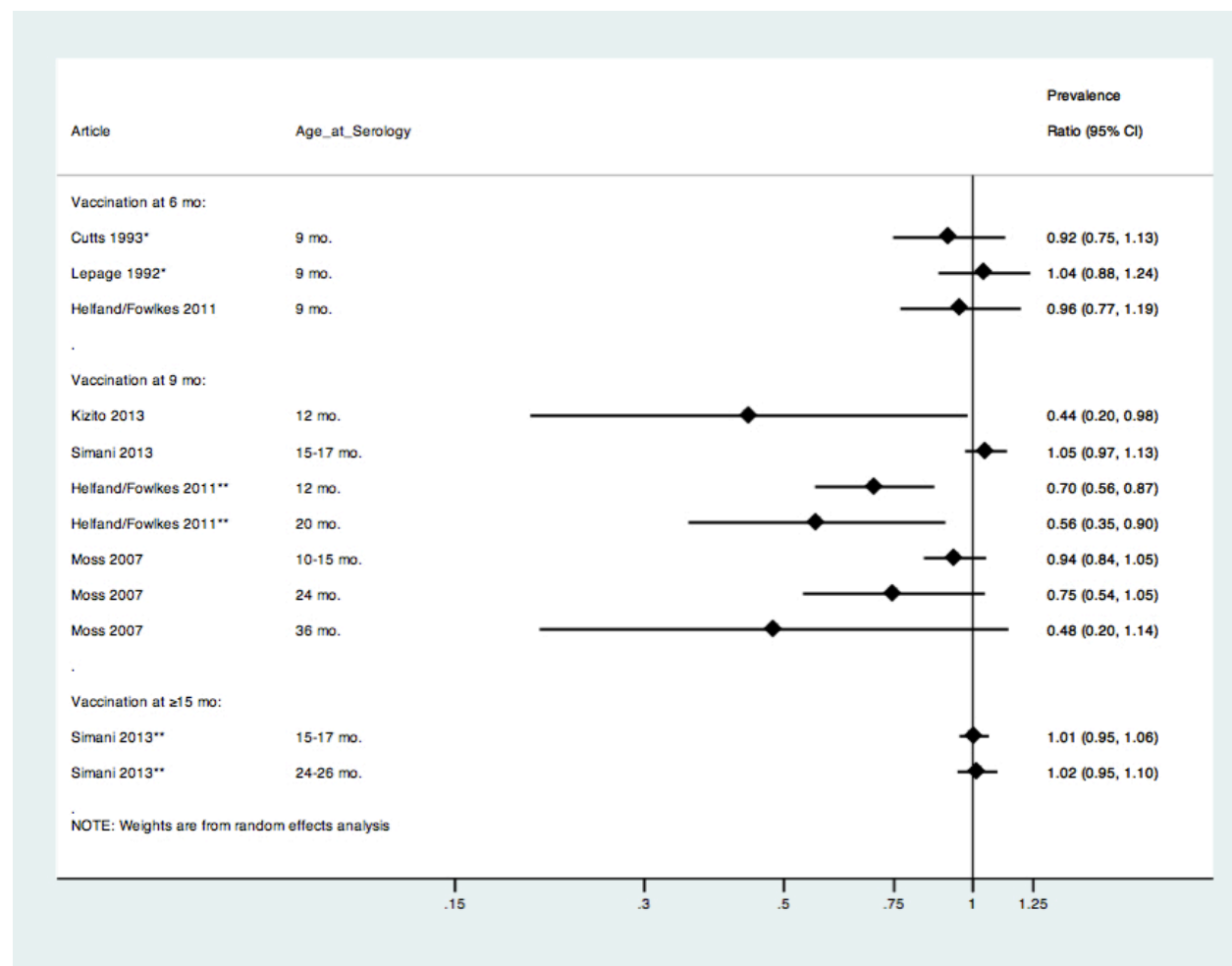
**Figure 3:** Updated systematic review of the safety and immunogenicity of measles vaccine in HIV-infected children



Systematic review conducted by Nicky Mehtani

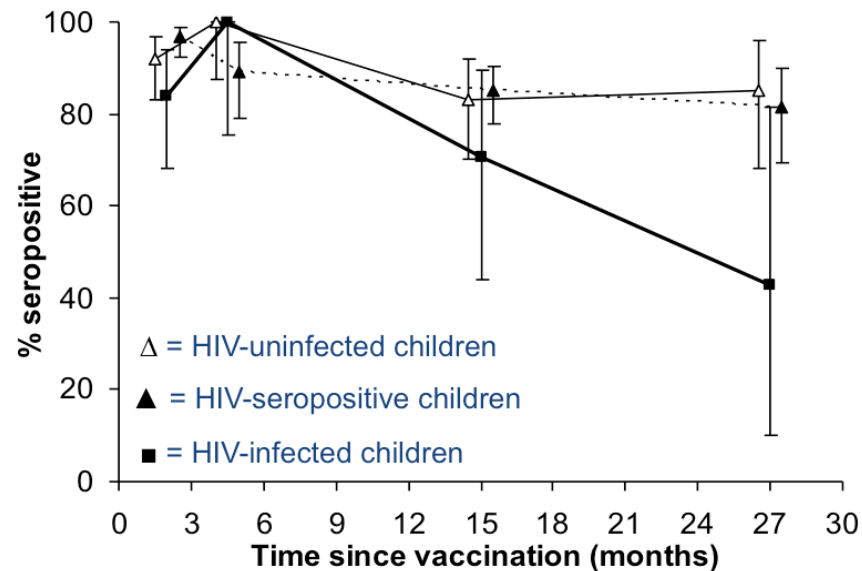


**Figure 4:** Seroprevalence ratios comparing measles seropositivity in HIV-infected to uninfected children following measles vaccination at 6, 9 and ≥15 months



Systematic review conducted by Nicky Mehtani

**Figure 5:** Waning measles seropositivity in HIV-infected children not receiving antiretroviral therapy and vaccinated at 9 months of age, compared to HIV-unexposed, uninfected and HIV-exposed, uninfected children. Measles antibodies were measured by plaque reduction neutralization assay.



Source: Moss WJ, Scott S, Mugala N, Ndhlovu Z, Beeler J, Audet S, Ngala M, Mwangala S, Nkonga-Mwangilwa C, Ryon JR, Monze M, Kasolo F, Quinn TC, Cousens S, Griffin DE, Cutts FT. Immunogenicity of standard-titre measles vaccine in HIV-1-infected and uninfected Zambian children: an observational study. *J Infect Dis* 2007;196:347-55.

**Table 1:** Measles seroprevalence after an additional dose of MCV in HIV-infected children receiving HAART

Reference	Country	No. of children	Age	Response to repeat immunization
Berkelhamer 2001	United States	14	2-11 y	<b>64%</b>
Melvin 2003	United States	18	3-14 y	<b>83%</b>
Farquhar 2009	Kenya	18	NA	<b>78%</b>
Aurpibul 2007, 2010	Thailand	51	Mean, 10.2 y	<b>90%</b> after 1 mos <b>85%</b> after 3 yrs
Abzug 2012	United States	193	2-19 yrs	<b>89%</b> at 8 weeks <b>80%</b> at 80 weeks
Rainwater 2013	Zambia	19	9-60 mos	<b>95%</b> of children receiving HAART